Residual Hypertriglyceridemia and Estimated Atherosclerotic Cardiovascular Disease Risk by Statin Use in U.S. Adults With Diabetes: National Health and Nutrition Examination Survey 2007-2014

Wenjun Fan,[1] Sephy Philip,[2] Craig Granowitz,[2] Peter P. Toth,[3,4] and Nathan D. Wong[1]

https://doi.org/10.2337/dc19-0501

OBJECTIVE

Hypertriglyceridemia (HTG) is common in patients with diabetes, and statins remain the first-line therapy. However, the proportion of patients with diabetes having elevated triglycerides (TGs) on statin treatment and their atherosclerotic cardiovascular disease (ASCVD) risk has not been described. We quantified the prevalence of HTG in U.S. adults with diabetes currently treated versus not treated with statins and the estimated 10-year ASCVD risk.

RESEARCH DESIGN AND METHODS

Among 1,448 U.S. adults aged 20 years and over with diabetes (projected to 24.4 million) in the 2007–2014 National Health and Nutrition Examination Survey (NHANES), we compared the prevalence of borderline HTG (TG 150–199 mg/dL) and HTG (TG ≥200 mg/dL) by statin use and LDL-C levels, and we used logistic regression to identify risk factors for HTG. We also estimated the 10-year ASCVD risk in those without prior ASCVD.

RESULTS

The prevalence of borderline HTG and HTG was 20.0% and 19.5%, respectively, in statin users, and 20.1% and 25.3%, respectively, in nonstatin users ($P < 0.0001$). Even among statin users with LDL-C <70 mg/dL, borderline HTG prevalence was 16.8%, and HTG prevalence was 16.7%. Approximately 77.5% of those with HTG had an estimated 10-year ASCVD risk of ≥7.5%, with almost 40% of statin users having ASCVD risk ≥20%.

CONCLUSIONS

Residual HTG occurs over one-fifth (~5.5 million) of U.S. adults with diabetes, including those on statin therapy and well-controlled LDL-C. Over three-quarters of adults with diabetes with HTG are at moderate or high 10-year risk for ASCVD. Greater efforts are needed to promote lifestyle and pharmacologic means to address residual HTG.

[1]Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, CA
[2]Medical Affairs, Amarin Pharma, Inc, Bedminster, NJ
[3]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
[4]Department of Preventive Cardiology, CGH Medical Center, Sterling, IL

Corresponding author: Nathan D. Wong, ndwong@uci.edu

Received 11 March 2019 and accepted 31 August 2019

Elevated blood triglycerides (TGs) are a common lipid disorder with borderline hypertriglyceridemia (HTG) between 150 and 199 mg/dL and HTG if defined as TG of at least 200 mg/dL. Approximately 25% of the U.S. population have TG levels of 150 mg/dL or greater (1,2). Patients with diabetes are more likely to have elevated TGs because of both hepatic overproduction of VLDL-C and reduced TG lipolysis due to decreased lipoprotein lipase activity (3). In the setting of insulin resistance, more free fatty acids reach the liver; one means of disposing of this fatty acid excess is to increase hepatic TG and VLDL production and secretion (4).

Epidemiological data on the prevalence of borderline or elevated TGs among patients with diabetes are limited, but earlier reports have indicated that it is prevalent in more than half of the U.S. population with diabetes (5). HTG is significantly associated with the risk of future cardiovascular disease (CVD) and is common in people with diabetes (6–8), even among those with well-controlled LDL-C levels on statin therapy (8).

However, while statins do reduce CVD risk in people with diabetes, substantial residual risk for CVD events remains (8,9), and few trials of TG-lowering agents have shown benefit. Previously, the VA HDL Intervention Trial (VA-HIT) showed people with diabetes receiving gemfibrozil had a 32% risk reduction in the composite end point of coronary heart disease (CHD) death, stroke, or myocardial infarction (MI) (10). Among patients with low LDL-C, elevations in plasma TGs increase CVD risk, and the greatest reduction in CVD risk occurs when both LDL and TGs are reduced (11). Although statins are currently the first-line treatment for patients with diabetes based on the most recent dyslipidemia guidelines (12), a substantial prevalence of elevated TG remains in patients with diabetes along with associated atherosclerotic CVD (ASCVD) risks despite statin treatment. Such information is important for understanding the role that newer therapies may play in reducing such risks.

The purpose of the current study is to estimate the proportion of people with borderline HTG and HTG among adults with diabetes in the U.S. with or without statin treatment, and further estimate their residual ASCVD risk in the following decade.

RESEARCH DESIGN AND METHODS

Study Sample

We included U.S. adults from the National Health and Nutrition Examination Survey (NHANES) 2007 to 2014. The methodology of NHANES data collection has been described elsewhere (13). Eligible participants for our analysis included adults aged 20 years and over, randomly assigned to a morning session that asked to be fasting for at least 8.5 hours, with available TG data. Participants were defined as having diabetes if one or more of the following criteria were met: *1*) fasting glucose $\geq$ 126 mg/dL; *2*) nonfasting glucose $\geq$200 mg/dL; *3*) taking medication to lower blood glucose; *4*) taking insulin; or *5*) HbA_{1c} $\geq$6.5% (48 mmol/mol). A total of 1,448 adults aged 20 years and over with diabetes (projected to 24.4 million U.S. population) were included in this study. Of those, 1,390 adults (projected to 23.4 million) had available LDL-C data and 889 adults (projected to 14.7 million) had complete information to calculate ASCVD risk score (described below).

Measurements

Examination and laboratory test results, medical history, and prescription medication information were used from the NHANES data. Obesity was defined as a BMI $\geq$30 kg/m^2. Hypertension was defined (based on the accepted definition at the time of the survey years) as a systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg or currently taking prescription medication for hypertension. Total cholesterol and TGs were assayed using enzymatic reactions on a Roche/Hitachi Modular P Chemistry Analyzer, while HDL-C was analyzed through a modified traditional multistep precipitation reaction. LDL-C was computed using the Friedewald equation (defined as total cholesterol minus HDL-C and TG/5 in mg/dL) (13). Chronic kidney disease was determined by estimated glomerular filtration rate $<$60 mL/min/1.73 m^2 using the CKD-EPI Eq ($GFR = 141 \times \min[Scr/\kappa, 1]^{\alpha} \times \max[Scr/\kappa, 1]^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1) (14). Information regarding smoking status, history of heart failure, CHD, stroke, and family history of heart attack were based on self-report. TG levels were classified as normal ($<$150 mg/dL), borderline high TG (TG 150–199 mg/dL), and HTG (TG $\geq$200 mg/dL), which is consistent with recent recommendations and statements (15–17).

Statistical Analyses

We first calculated the weighted proportion and number of patients with diabetes within each TG category ($<$150, 150–199, $\geq$200 mg/dL) with and without statin use in NHANES 2007–2014 and further stratified by sex and ethnicity. The χ^2 test was applied to determine whether the distributions were significantly different between groups. We also compared the distribution of demographic characteristics and proportion of cardiovascular risk factors in those with normal TG ($<$150 mg/dL), borderline HTG (TG 150–199 mg/dL), and HTG (TG $\geq$200 mg/dL), including age, sex, ethnicity, obesity, smoking status, hypertension, history of CHD, heart failure, stroke, chronic kidney disease, and family history of heart attack. In the overall sample of patients with diabetes, the proportion of adults with borderline HTG and HTG according to these cut points by LDL-C category ($<$70, 70–99, 100–129, 130–159, and $\geq$160 mg/dL) was also evaluated according to statin use. In addition, of interest is the prevalence of atherogenic dyslipidemia indicated by a TG $\geq$200 and HDL-C $<$35 mg/dL, which we had also evaluated according to statin use.

Next, the American College of Cardiology/American Heart Association pooled cohort 10-year ASCVD risk score (%) was determined for participants according to TG categories and was reported as the proportion of those with scores $<$5%, 5–7.4%, 7.5–19.9%, and $\geq$20.0%, respectively. The variables used for ASCVD risk score calculation included age, sex, race, systolic blood pressure, total cholesterol, HDL-C, diabetes status, smoking status, and antihypertensive treatment. The risk score was only calculated among those without prior ASCVD (CHD, MI, stroke, and angina) and aged between 40 and 79 years old. The same procedure was then repeated among statin users.

Lastly, multiple logistic regression analyses with stepwise selection were

performed to identify the independent predictors of TG ≥150 mg/dL among our statin-treated patients with diabetes. Initially, we included age, sex, ethnicity, BMI, HDL-C, LDL-C, cigarette smoking, hypertension, heart failure, CHD, stroke, and family history of heart attack as potential risk factors, and those who satisfied α-to-enter and α-to-stay levels of 0.15 (*P* values to allow entry and retaining of variables, respectively) were included in our final models through stepwise selection procedures (age, sex, and ethnicity were forced into final models).

All analyses applied an NHANES 8-year sample weighting procedure to project to the U.S. population in millions. SAS version 9.3 was used for data analysis.

RESULTS

In our sample of 1,448 participants with diabetes (weighted to 24.4 million) from NHANES 2007–2014, the overall prevalence of borderline HTG was 20.1% (projected to 4.9 million) and HTG was 22.5% (projected to 5.5 million). Approximately 19.5% and 25.3% in statin and nonstatin users had HTG, respectively. Specifically, the proportions of subjects with TG levels of <150, 150–199, ≥200 mg/dL were 60.5% (7.5 million), 20.0% (2.5 million), 19.5% (2.4 million) and 54.6% (6.6 million), 20.1% (2.4 million), 25.3% (3.0 million) in those with versus those without statin treatment, respectively ($P < 0.0001$). Compared with subjects with normal TG levels, those with borderline HTG and HTG were somewhat younger (mean age 59.2, 57.8 vs. 60.8 years, $P < 0.0001$), less likely to be non-Hispanic black (8.5%, 8.0% vs. 19.2%, $P < 0.0001$), more likely to have obesity (73.1%, 65.1% vs. 54.5%, $P < 0.0001$), and currently smoking (12.2%, 22.4% vs. 11.8%, $P = 0.0011$) (Table 1).

The prevalences of HTG were 17.4% and 22.1% among male and female statin users, respectively, while in those without statin use, the prevalences were 25.6% and 24.9%, respectively (sex differences not significant). In both statin and nonstatin users, Hispanics had more than twice the prevalence of HTG than non-Hispanic blacks (28.1% vs. 9.9%; 32.2% vs. 14.4%; ethnic differences were significant among nonstatin users with *P* value = 0.0047, but not significant among statin users) (Fig. 1*A* and *B*). In those with LDL-C <70 mg/dL, 16.7% had HTG; these proportions were 15.4%, 22.0%, 15.9%, and 28.6% with higher LDL-C levels of 70–99, 100–129, 130–159, and ≥160 mg/dL. Among nonstatin users, HTG was present in 11.5%, 23.2%, 9.2%, 31.4%, and 39.0% among these LDL-C groups, respectively ($P < 0.0001$) (Fig. 2). Finally, we examined the prevalence of atherogenic dyslipidemia in our sample of diabetes patients indicated by a TG ≥200 mg/dL and HDL-C <35 mg/dL according to statin use. This prevalence was 3.9% (extrapolating to 1.0 million) and 3.3% (0.8 million) among nonstatin and statin users, respectively.

The majority of diabetes patients had 10-year estimated ASCVD risks ≥7.5%, with proportions of 68.7%, 62.7%, and 77.5% in the normal TG, borderline HTG, and HTG groups, respectively. The proportions were even greater among those on statin treatment, with over 85% of HTG individuals with diabetes at high risk of ASCVD over the next decade. One-third of patients with diabetes with HTG overall and ~40% of statin users were at high ASCVD risk (≥20%) (Fig. 3). Mean 10-year ASCVD risks were 15.4, 17.0, and 17.1 among those not on statins, and 19.2, 19.0, and 20.7 among those on statins in the normal TG, borderline high TG, and HTG groups, respectively ($P = 0.6078$ across TG categories for both those on and not on statins).

Table 2 shows results for our logistic regression analysis. Variables remained after stepwise selection in predicting TG ≥150 mg/dL were age, sex, ethnicity, HDL-C, and LDL-C. Results from multiple logistic regression models showed that among statin-treated patients with diabetes, female sex was independently associated with an 88% higher risk of having TG ≥150 mg/dL (odds ratio [OR] = 1.88, 95% CI = 1.02–3.48, $P < 0.01$) and those of non-Hispanic black ancestry having nearly a two-thirds lower likelihood of having TG ≥150 mg/dL (OR = 0.34, 95% CI = 0.17–0.69, $P < 0.01$) compared with non-Hispanic whites. Higher HDL-C was significantly associated with lower risk of TG ≥150 mg/dL (OR = 0.45 per standard deviation, 95% CI = 0.31–0.65, $P < 0.0001$). All the other covariates were not significantly associated with elevated TG.

CONCLUSIONS

To our knowledge, this study is unique in examining the prevalence of residual HTG despite statin therapy among a U.S. population–representative sample of adults with diabetes. We found that ~40% of patients with diabetes have mild elevations in TG levels of ≥150 mg/dL, with half of these having levels of ≥200 mg/dL, regardless of statin use. No significant difference is observed between males and females with or without statin use. Of interest, among those on statin treatment despite having LDL-C <100 mg/dL, more than one-third of patients with diabetes have borderline HTG or HTG. Almost 40% of patients with diabetes and mild to moderate elevations of TG are at moderate or high risk for ASCVD in the following 10 years. In addition, about half of statin users with mild to moderate elevations of TG are at high risk for ASCVD. Finally, we note that despite statin treatment, among our U.S. sample of adults with diabetes, females have nearly double the likelihood of having HTG compared with males, and people of African American ancestry have nearly a two-thirds lower likelihood of having HTG compared with whites.

In part because of greater efforts at promoting lifestyle modification, the prevalence of borderline HTG or HTG (≥150 mg/dL) in people with diabetes has decreased from over 50% in NHANES 2009–2010 (4) to closer to 40% from more recent NHANES surveys as presented in the current study. However, the relatively large numbers of U.S. adults with diabetes who still have HTG is striking especially among certain minority groups. Hispanics have the highest prevalence of HTG, while non-Hispanic blacks have the lowest. A study using electronic health records data from California, which has a comprehensive representation of multiple ethnic groups, also demonstrates the HTG prevalence has doubled among Hispanics compared with blacks in both males and females (18). Also, the mean TG level is almost 50% higher in Mexican Americans than in non-Hispanic blacks (19). The "TG paradox" of non-Hispanic blacks with diabetes with normal TG has been under investigation for years. Major arguments have focused on the role of lipoprotein lipase. A greater activity and less inhibition of lipoprotein lipase is observed in non-Hispanic blacks with diabetes, which may explain the paradox (20). Hispanics generally appear to

Table 1—Demographic characteristics among U.S. adults with diabetes, NHANES 2007–2014

	Total (n = 1,448, N = 24.4 million)	Normal TG: TG <150 mg/dL (n = 867, 14.0 million, 57.4%)	Borderline HTG: TG 150–199 mg/dL (n = 255, 4.9 million, 20.1%)	HTG: TG ≥200 mg/dL (n = 326, 5.5 million, 22.5%)	P Value
Age, years	59.8 ± 0.4	60.8 ± 0.5	59.2 ± 0.9	57.8 ± 0.8	<0.0001
Female sex	699 (12.0 million, 49.4%)	412 (6.7 million, 47.8%)	131 (2.5 million, 51.0%)	156 (2.8 million, 52.1%)	0.5290
Ethnicity					
Mexican American	255 (2.3 million, 9.6%)	133 (1.2 million, 8.4%)	51 (0.5 million, 9.8%)	71 (0.7 million, 12.1%)	<0.0001
Other Hispanic	162 (1.5 million, 6.0%)	82 (0.7 million, 4.8%)	28 (0.3 million, 5.8%)	52 (0.5 million, 9.2%)	
Non-Hispanic white	562 (15.1 million, 61.7%)	311 (8.5 million, 60.2%)	112 (3.2 million, 65.8%)	139 (3.4 million, 62.0%)	
Non-Hispanic black	338 (3.5 million, 14.5%)	265 (2.7 million, 19.2%)	36 (0.4 million, 8.5%)	37 (0.4 million, 8.0%)	
Other Race	131 (2.0 million, 8.2%)	76 (1.0 million, 7.4%)	28 (0.5 million, 10.1%)	27 (0.5M, 8.7%)	
BMI (kg/m^2)	32.9 ± 0.3	32.0 ± 0.3	34.8 ± 0.7	33.8 ± 0.4	0.0103
Obesity	811 (14.8 million, 60.6%)	459 (7.6 million, 54.5%)	161 (3.6 million, 73.1%)	191 (3.5 million, 65.1%)	<0.0001
Current cigarette smoking	221 (3.5 million, 14.3%)	114 (1.6 million, 11.8%)	38 (0.6 million, 12.2%)	69 (1.2 million, 22.4%)	0.0011
On statin	730 (12.4 million, 50.7%)	464 (7.5 million, 53.2%)	131 (2.5 million, 50.5%)	135 (2.4 million, 44.3%)	0.0920
Heart failure	135 (2.3 million, 9.5%)	77 (1.2 million, 8.4%)	26 (0.5 million, 9.6%)	32 (0.7 million, 12.4%)	0.2790
CHD	157 (2.8 million, 11.7%)	89 (1.6 million, 11.3%)	32 (0.6 million, 12.6%)	36 (0.6 million, 11.7%)	0.8900
Hypertension	1029 (17.2 million, 71.9%)	619 (9.6 million, 69.7%)	184 (3.7 million, 76.9%)	226 (3.9 million, 73.0%)	0.1777
Stroke	124 (2.0 million, 8.4%)	74 (1.2 million, 8.2%)	22 (0.3 million, 7.1%)	28 (0.5 million, 9.8%)	0.5949
CKD	149 (2.6 million, 20.5%)	98 (1.7 million, 22.0%)	22 (0.5 million, 19.9%)	29 (0.5 million, 17.3%)	0.5710
Family history of heart attack	211 (3.9 million, 16.1%)	108 (1.9 million, 13.7%)	47 (0.9 million, 18.9%)	56 (1.1 million, 19.7%)	0.1100

Numbers are presented as unweighted number (weighted number, weighted proportion) for categorical variables and weighted means ±SE for continuous variables. HTG is defined as fasting TG ≥200 mg/dL. P values represented are across all three groups (normal, borderline, and HTG). CKD, chronic kidney disease.

be more likely to have HTG regardless of the presence of diabetes, and there is evidence suggesting a genetic predisposition to HTG (19). Nevertheless, more efforts are needed to investigate the etiology, prevention, and treatment of HTG in ethnic minority groups.

Our results also suggest that only half of patients with diabetes in the U.S. are on statin treatment, and of those, 40% have borderline HTG or HTG in 2007–2014. It is not known whether levels have changed significantly since this period. According to the American Diabetes Association guidelines, moderate or high intensity statin therapy should be initiated in patients with diabetes with prior CVD or those aged 40 years and older with one or more CVD risk factors, and moderate intensity statin therapy can be considered in younger people with other ASCVD risk factors (21). In addition, statin therapy remains the first-line therapy for those patients according to guidelines from the National Lipid Association and the American Heart Association (12). Our results also indicate that more than one-third of those on statins with well-controlled LDL-C still have borderline high TG or HTG. Conversely, what we show is a substantial prevalence of HTG and especially borderline high TG in those on statins whose LDL-C remains at 160 mg/dL or higher. While we do not have pretreatment levels of LDL-C and TG, we could speculate at least in some people both the remaining elevated LDL-C and TG may be because of nonresponse to the statin or an inadequate dosage. This constitutes a significant opportunity to address this residual HTG in statin-treated adults with diabetes.

The high prevalence of CVD in individuals with diabetes and HTG has been investigated for several decades. One meta-analysis involving a total of 10,158 patients with incident coronary artery disease from 262,525 participants in 29 studies shows that a moderately strong association was consistently observed between TG concentration and risk of coronary artery disease (7). More recently, longitudinal, real-world administrative database analyses report increased CVD risk and direct healthcare costs associated with HTG despite statin therapy and controlled LDL-C compared with those with TG ≥150 mg/dL (8).

We also note the majority of those with diabetes who have HTG, even while on a statin, are at moderate or high risk of an ASCVD event in the next decade. Current guidelines (12) recommend at least a moderate intensity statin in all those with diabetes, and high intensity statin therapy for the many who have multiple risk factors. Ensuring recommended statin dosages is a first-line therapy for optimizing ASCVD risk

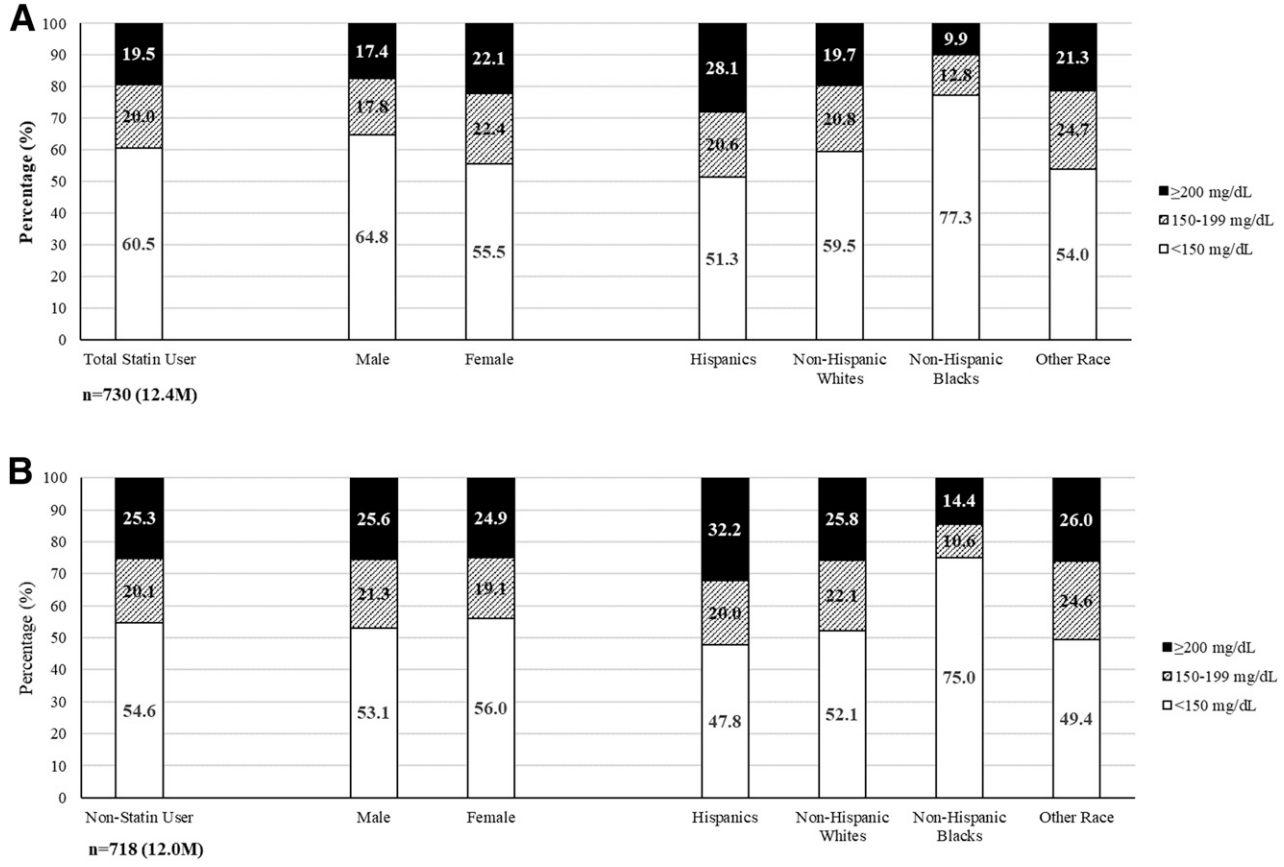

Figure 1—Estimated proportions of adults by sex and ethnicity with different levels of TG among those with diabetes, NHANES 2007–2014 among statin users (*A*) and those not using statins (*B*). Numbers represented weighted proportion within each group. $P < 0.01$ in those not using statins across ethnic groups.

reduction, including for people with diabetes regardless of TG levels. While the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial showed that adding fenofibrate as an adjuvant therapy to simvastatin failed to meet its primary end point in reducing ASCVD events (22), those with HTG and low HDL-C did show a 31% risk reduction that was of borderline significance ($P = 0.06$) and in Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial, this subgroup also showed a borderline significant ($P = 0.07$) 26% risk reduction (23). However, the potential benefit in the HTG and low HDL-C subgroups from ACCORD Lipid and AIM-HIGH can only be thought of as hypothesis generating as those trials missed their primary cardiovascular end points. Recently, the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) showed that patients with ASCVD or diabetes and additional CV risk factors treated with 4 g/day of icosapent ethyl (prescription eicosapentaenoic acid [EPA] omega-3 fatty acid) in addition to statins (compared with statins alone) are 25% less likely to have future ASCVD events over a median of 4.9 years follow-up. This study included people mainly with TG of 200 mg/dL or greater, although initially a lower TG inclusion of 150 mg/dL with a 10% allowed variability around this resulted in patients with baseline TG as low as 135 mg/dL. Moreover, from subgroup analyses, those participants with diabetes had a similar 23% (hazard ratio = 0.77, 95% CI = 0.68–0.87) and 30% (hazard ratio = 0.70, 95% CI = 0.60–0.81) lower risk in the primary and key secondary end points (24), demonstrating similar benefits as in those without diabetes. Also, whether or not on treatment TGs were ≥150 mg/dL or <150 mg/dL, there was similar benefit, suggesting that other non-TG-lowering effects of icosapent ethyl may have had an impact. Whether the risk reductions seen in REDUCE-IT are truly unique to icosapent ethyl pure EPA is still an open question. While recent trials of combined EPA/docosahexaenoic acid have not shown benefit over statin therapy, possibly because of inadequate dosages used, the currently ongoing Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients With Hypertriglyceridemia (STRENGTH) trial (25) involving a 4 g per day EPA/docosahexaenoic acid combination product is due to report out in the near future. In addition, the ongoing Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes (PROMINENT) trial will examine the efficacy of pemafibrate in reducing cardiovascular outcomes in ~10,000 patients with both diabetes and atherogenic dyslipidemia (HTG and low HDL-C), as well as investigations of apolipoprotein CIII inhibitors and angiopoietin-like 3 protein inhibitors will further examine the efficacy of modifying dyslipidemia in patients with diabetes in reducing residual ASCVD risk (26).

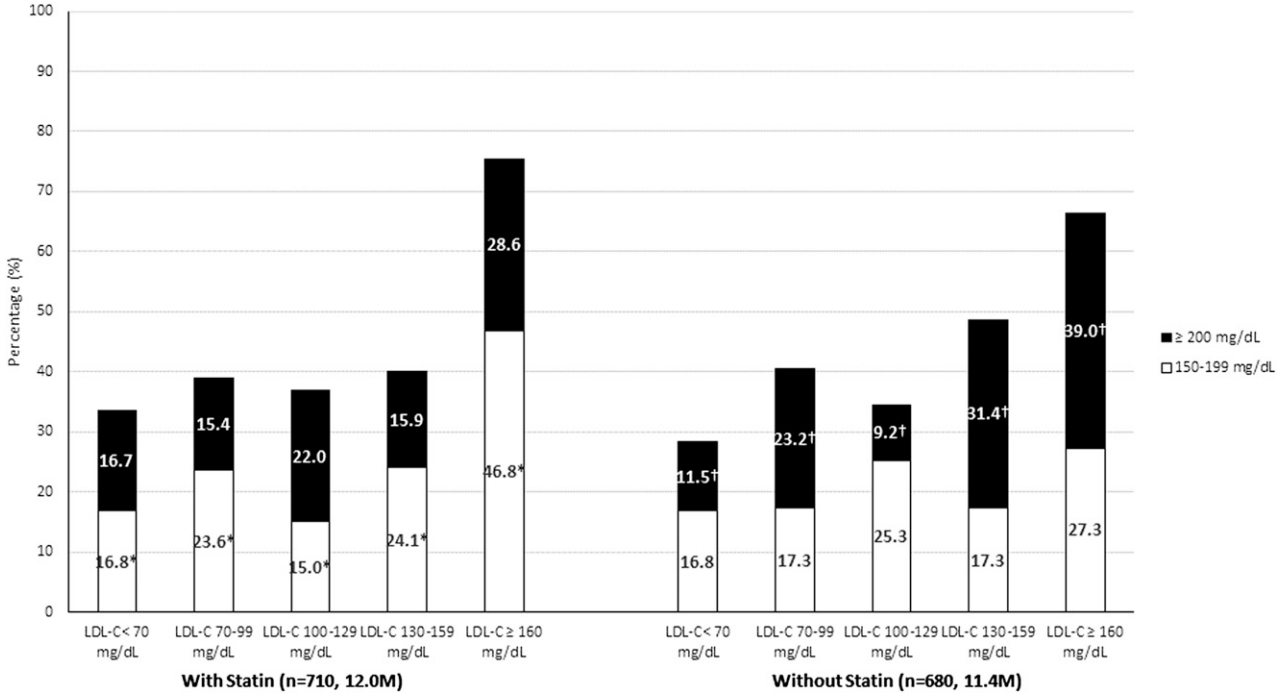

Figure 2—Proportion of adults with diabetes with elevated TGs according to LDL-C, NHANES 2007–2014 sample limited to those with nonmissing LDL-C data. *P* value was calculated comparing the proportion of elevated TGs across LDL-C levels within statin and nonstatin users. For those who were on statin treatment ($n = 710$), 29.7% had LDL-C <70 mg/dL; 42.1% had LDL-C <100 mg/dL; 20.1% had 100–129 mg/dL; 5.5% had 130–159 mg/dL; and 2.6% had >160 mg/dL. For those not on statins ($n = 680$), respective proportions were 6.9%, 24.4%, 35.6%, 21.4%, and 11.7%. *$P = 0.0386$ comparing the weighted proportion of TGs 150–199 mg/dL across all LDL-C categories among statin users. †$P < 0.0001$ comparing the weighted proportion of TG ≥200 mg/dL across all LDL-C categories among nonstatin users.

While recent cholesterol management guidelines have not recommended nonstatin therapies for people with moderate HTG (12), the American Diabetes Association recently revised its 2019 Standards of Diabetes Care, providing a class A recommendation for consideration of icosapent ethyl treatment in patients with diabetes on a statin with controlled LDL-C who have either ASCVD or multiple risk factors and TGs of 135–499 mg/dL (27).

There are several strengths and limitations in our study. A key strength of NHANES is its ability to use sample weighting to estimate the millions of U.S. adults with diabetes who have remaining HTG both among statin users

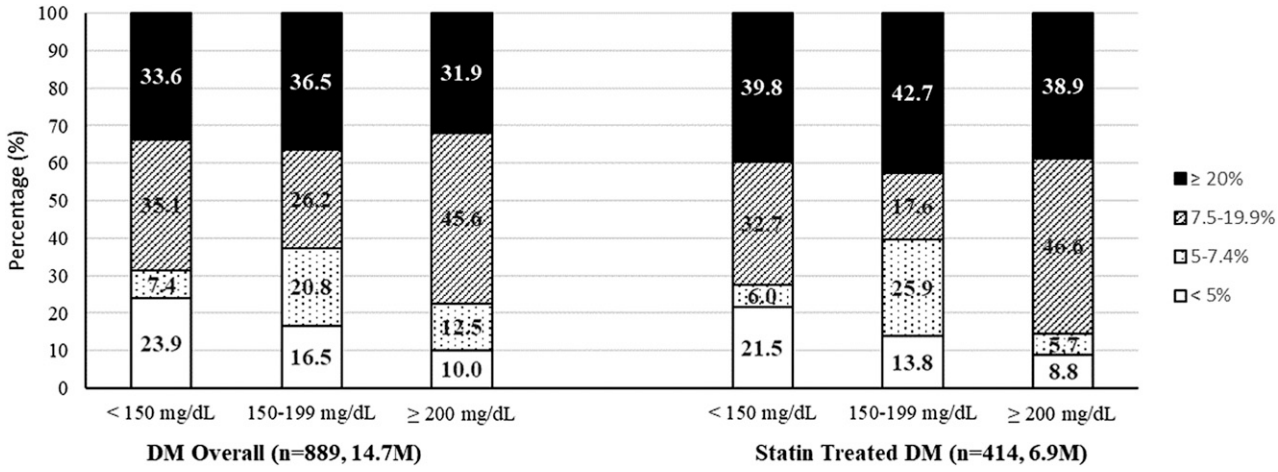

Figure 3—Estimated proportions of adults with diabetes with different levels of ACC/AHA pooled cohort 10-year ASCVD risk score (%) among TG groups stratified by statin use, NHANES 2007–2014. From the original sample of 1,448 subjects, we excluded 245 subjects who were younger than age of 40 years or older than 79 years and further excluded 287 subjects with prior CVD (heart attack, CHD, stroke, and angina). An additional 27 subjects with missing systolic blood pressure values were further eliminated, which made the final sample of 889 for analysis. Of these 889 patients, 414 were on statin treatment. $P = 0.0003$ (weighted) for comparing proportion of ACC/AHA pooled cohort 10-year ASCVD risk score categories among TG levels in diabetes patients overall. $P > 0.05$ (weighted) for comparing proportion of ACC/AHA pooled cohort 10-year ASCVD risk score categories among TG levels in statin-treated diabetes patients. ACC, American College of Cardiology; AHA, American Heart Association.

Table 2—Multiple logistic regression in predicting TG ≥150 mg/dL among statin-treated individuals with diabetes, NHANES 2007–2014

	OR for TG ≥150 mg/dL
Age (unit of 10 years)	0.97 (0.76–1.22)
Sex (female vs. male)	1.88 (1.02–3.48)*
Ethnicity	
Non-Hispanic white	1.00
Mexican American	1.87 (0.81–4.34)
Other Hispanic	0.88 (0.39–2.00)
Non-Hispanic black	0.34 (0.17–0.69)*
Other races	0.99 (0.41–2.40)
HDL-C	0.45 (0.31–0.65)†
LDL-C	1.31 (0.99–1.72)

Stepwise selection procedure: α-to-enter = 0.15, α-to-stay = 0.15. Final variables remained after stepwise selection in predicting TG ≥150 mg/dL were age, sex, ethnicity, HDL-C, and LDL-C. Age, sex and ethnicity were forced into in the model. HDL-C and LDL-C were standardized with a standard deviation of 15.68 and 35.22, respectively. *$P < 0.01$. †$P < 0.001$.

and nonusers. NHANES also has uniform ascertainment of medical history and measurement of lipids and other risk factors across all study centers. Although NHANES relies on self-reported medical history information, previous investigations have shown a close correspondence with patients' actual medical history (28). However, a limitation of NHANES is the unavailability of follow-up for ASCVD events because of its nature of having a cross-sectional study design. In addition, the event estimates only apply to those adults with diabetes aged 40–79 years without preexisting ASCVD and with complete data on necessary variables for the calculation of ASCVD risk; thus, potential underestimation of events may exist because of missing data on covariates and/or events occurring outside these parameters. Furthermore, no information regarding the duration, intensity, and adherence of statin use is available in NHANES; thus, it is impossible to evaluate how our results would be different based on a fixed dosage or intensity of a given statin. Finally, while we have defined borderline HTG and HTG at cut points of 150 mg/dL and 200 mg/dL, respectively, consistent with terminology from several societies and statements (15–17), not all societies use the same terminology or cut points. For example, the 2019 American Diabetes Association Standards of Care (21) notes elevated TGs to be 150 mg/dL or higher and moderate HTG as 175–499 mg/dL.

In conclusion, our study reveals that almost one in five adults with diabetes in the U.S. has residual HTG despite statin use. Moreover, many of these people are at moderate or increased risk of future ASCVD events in the next decade. This warrants greater attention toward improved efforts such as lifestyle management as the cornerstone for managing dyslipidemia, as well as consideration of newer evidence-based therapies to reduce residual ASCVD risk that remains despite statin-controlled LDL-C.

Duality of Interest. This project was supported by a contract from Amarin Pharma, Inc. to the University of California, Irvine, CA. N.D.W. receives research support from Amarin, Amgen, Boehringer-Ingelheim, and Novo Nordisk; is on the speaker's bureau for Sanofi and Amarin; and is a consultant or on the advisory board for Amarin, Novartis, and Astra-Zeneca. S.P. and C.G. are employed at Amarin Pharma, Inc. P.P.T. is on the speaker's bureau for Amarin, Amgen, Kowa, Nova Nordisk, Regeneron, and Sanofi and is a consultant or on the advisory board for Amarin, Amgen, Kowa, Nova Nordisk, Regeneron, and Sanofi.

Author Contributions. W.F. and N.D.W. wrote the manuscript and conducted the analysis. S.P., C.G., and P.P.T. provided critical review, comment, and editorial suggestions. W.F., S.P., C.G., P.P.T., and N.D.W. have approved and determined the final manuscript to be accurate. N.D.W. is the guarantor of the study and takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Prior Presentation. Parts of this work were presented at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

References

1. Fan W, Philip S, Granowitz C, Toth PP, Wong ND. Hypertriglyceridemia in statin-treated US adults: the National Health and Nutrition Examination Survey. J Clin Lipidol 2019;13:100–108
2. Carroll MD, Kit BK, Lacher DA. *Trends in Elevated Triglyceride in Adults: United States, 2001–2012. NCHS Data Brief, no 198*, Hyattsville, MD, National Center for Health Statistics, 2015
3. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia 2015;58:886–899
4. St-Pierre J, Lemieux I, Perron P, et al. Relation of the "hypertriglyceridemic waist" phenotype to earlier manifestations of coronary artery disease in patients with glucose intolerance and type 2 diabetes mellitus. Am J Cardiol 2007;99:369–373
5. Jacobs MJ, Kleisli T, Pio JR, et al. Prevalence and control of dyslipidemia among persons with diabetes in the United States. Diabetes Res Clin Pract 2005;70:263–269
6. Tada H, Kawashiri MA, Nomura A, et al. Serum triglycerides predict first cardiovascular events in diabetic patients with hypercholesterolemia and retinopathy. Eur J Prev Cardiol 2018;25:1852–1860
7. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007;115:450–458
8. Nichols GA, Philip S, Reynolds K, Granowitz CB, Fazio S. Increased residual cardiovascular risk in patients with diabetes and high versus normal triglycerides despite statin-controlled LDL cholesterol. Diabetes Obes Metab 2019;21:366–371
9. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutr Metab Cardiovasc Dis 2013;23:799–807
10. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597–2604
11. Otvos JD, Collins D, Freedman DS, et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. Circulation 2006;113:1556–1563
12. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation 2019;139:e1182–e1186]. Circulation 2019;139:e1082–e1143
13. Centers for Disease Control and Prevention. 2007: National Health and Nutrition Examination Survey (NHANES) [Internet]. U.S. Department of Health and Human Services, 2007. Available from https://wwwn.cdc.gov/nchs/data/nhanes/2007-2008/manuals/manual_lab.pdf. Accessed 20 February 2019
14. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612

15. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol 2014;8: 473–488
16. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23(Suppl. 2):1–87
17. Miller M, Stone NJ, Ballantyne C, et al.; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011; 123:2292–2333
18. Frank AT, Zhao B, Jose PO, Azar KM, Fortmann SP, Palaniappan LP. Racial/ethnic differences in dyslipidemia patterns. Circulation 2014;129:570–579
19. Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. Atherosclerosis 2008;196:696–703
20. Yu SS, Castillo DC, Courville AB, Sumner AE. The triglyceride paradox in people of African descent. Metab Syndr Relat Disord 2012;10:77–82
21. American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of medical Care in diabetes-2019*. Diabetes Care 2019;42(Suppl. 1):S103–S123
22. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group.Effects of combination lipid therapy in type 2 diabetes mellitus [published correction appears in N Engl J Med 2010; 362:1748]. N Engl J Med 2010;362:1563–1574
23. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes). J Am Coll Cardiol 2013;62: 1580–1584
24. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22
25. Nicholls SJ, Lincoff AM, Bash D, et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. Clin Cardiol 2018;41:1281–1288
26. Alexopoulos AS, Qamar A, Hutchins K, Crowley MJ, Batch BC, Guyton JR. Triglycerides: emerging targets in diabetes care? Review of moderate hypertriglyceridemia in diabetes. Curr Diab Rep 2019;19:13
27. Living Standards of Medical Care in Diabetes. Available from http://care.diabetesjournals.org/living-standards. Accessed 6 June 2019
28. Vargas CM, Burt VL, Gillum RF, Pamuk ER. Validity of self-reported hypertension in the National Health and Nutrition Examination Survey III, 1988-1991. Prev Med 1997;26:678–685